REMARKS

The August 1, 2001 Official Action and the references cited therein have been carefully considered. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set forth in the August 1, 2001 Official Action. The initial due date for response, therefore, was November 1, 2001. A petition for a one (1) month extension of the response period is presented with this response, which is being filed within the one (1) month extension period, as December 1, 2001 fell on a Saturday.

In the August 1, 2001 Official Action, claims 1-18 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. The Examiner has rejected all claims based on the recitation of "between surfactant hydrophobic groups" in claim 1. Also in this connection, the Examiner has noted misspellings of certain terms in claims 8, 11 and 15.

Claims 1-18 are further rejected under 35 U.S.C. §103(a) as allegedly obvious based on the combined disclosures of U.S. Patent No. 5,410,016 to Hubbell et al. (hereinafter "Hubbell"), U.S. Patent No. 5,112,611 to Ahmad et al. (hereinafter "Ahmad"), U.S. Patent No. 5,531,917 to Nakayama et al. (hereinafter "Nakayama") and U.S. Patent No. 5,171,737 to Weiner et al. (hereinafter "Weiner"). According to the Examiner,

it would have been prima facie obvious to one of ordinary skill in the art at the time the present invention was made to deliver papain using the biodegradable hydrogels of Hubbell to achieve the beneficial effect of aiding human digestion, as purportedly suggested by Ahmad, and to add surfactants to achieve the beneficial effect of stabilizing the enzyme, as purportedly suggested by Nakayama. The Examiner further contends in this connection that the claimed complex would inherently form during mixing of the components to make the composition allegedly suggested by the cited prior art references.

Regarding the claimed non-ionic surfactants, the Examiner asserts that one of ordinary skill in the art would use dioleoyl phosphatidylethanolamine (DOPE) or dioleoyl phosphatidylcholine (DOPC) because of their utility for delivering bioactive agents, as purportedly suggested by Weiner.

Claims 2-5, 7-12 and 14 and 15 have been provisionally rejected under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 3-14 in applicants' co-pending Application No. 09/445,653 (hereinafter the '653 application).

Claim 1 has also been provisionally rejected on the ground of obviousness-type double patenting based on claim 1 of the '653 application.

In addition to the above-noted rejections, the Examiner has required submission of an abstract on a separate sheet, as required by 37 C.F.R. §1.72(b).

The aforementioned rejections and objection constitute the only grounds set forth in the August 1, 2001 Official Action for refusing allowance of this application.

In accordance with the present amendments, claims 8, 11 and 15 have been amended to correct the misspellings noted by the Examiner. Claim 15 has been further amended to remedy a lack of antecedent basis for the recitation "said anionic surfactant" in claim 12.

Also in accordance with the present amendments, an "Abstract of the Disclosure", in conformity with the requirements of 37 C.F.R. §1.72(b), is submitted herewith.

No new matter has been introduced into this application by any of the amendments presented herewith. Moreover, none of the present claim amendments are believed to constitute a surrender of any originally claimed subject matter in order to establish patentability.

For the reasons set forth below, applicants respectfully submit that each of the substantive grounds of rejection set forth in the August 1, 2001 Official Action is factually or legally deficient, or both. Those grounds of rejection are, therefore, respectfully traversed.

A. Claims 1-18 Fully Comply with the Definiteness Requirement of 35 U.S.C. §112, Second Paragraph

The relevant inquiry in determining compliance with the definiteness requirement of 35 U.S.C. §112, second paragraph, is whether the claim in question sets out and circumscribes a

particular area with a sufficient degree of precision and particularity, such that the metes and bounds of the claimed invention are reasonably clear. In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971).

The definiteness of claim language may not be analyzed in the abstract, but must be considered in light of the supporting specification, with the language in question being accorded the broadest reasonable interpretation consistent with its ordinary usage in the art. In re Morris, 44 U.S.P.Q.2d 1023, 1027 (Fed. Cir. 1997). See also Ex parte Cole, 223 U.S.P.Q. 94 (Bd. Apps. 1983) (claims are addressed to the person of average skill in a particular art; compliance with §112 must be adjudged from that perspective, not in a vacuum).

Furthermore, it has long been held that the initial burden of establishing a failure to comply with 35 U.S.C. §112, second paragraph, rests upon the Examiner. In rejecting a claim for alleged indefiniteness, therefore, it is incumbent upon the Examiner to establish that one having ordinary skill in the art would not have been able to ascertain the scope of protection defined by the claim when read in light of the supporting specification. Ex parte Cordova, 10 U.S.P.Q.2d 1949, 1952 (PTO B.P.A.I. 1988).

When the appropriate procedural approach is followed in assessing the claim terminology at issue herein, in accordance with the above-noted authorities, it is beyond question that applicants have satisfied the definiteness requirement of §112,

second paragraph, with respect to the subject matter of claims 1-18.

The claim recitation in question ("between surfactant hydrophobic groups") refers to the cooperative stabilization of the supramolecular complex of the invention resulting from the interaction between the hydrophobic groups present on the charged surfactant, which constitutes one of the components of the complex. "Surfactant" and "hydrophobic groups" are terms of art, the meanings of which are well understood by those of ordinary skill in the art. Grant & Hackh's Chemical Dictionary, 5th Ed., at 564 (copy attached) provides the following definition of surfactant:

> A surface-active agent; i.e., one that modifies the nature of surfaces, this often involving reducing the surface tension of water.

"Hydrophobic" and "group" are defined at pages 293 and 270, respectively, of Grant & Hackh's Chemical Dictionary, 5th Ed., (copies attached). "Hydrophobic" describes a substance that does not adsorb or absorb water. "Group" is an alternative expression for "radical". Applicants' respectfully submit that these definitions establish the broadest reasonable meaning that can be ascribed to the expression "between surfactant hydrophobic groups," based on ordinary usage as understood by those of ordinary skill in the art.

Furthermore, when the challenged claim recitation is properly considered in light of the specification, it cannot reasonably be considered vague. Directing attention to page 11,

lines 27-35, it is disclosed that the interactions of hydrophobic groups of surfactant molecules with each other contribute to cooperative stabilization of the ionic complexes formed between the block copolymers and surfactants of the opposite charge, which make up the composition of the invention. The phenomenon referred to in the present specification as "cooperative stabilization" is further explained at pages 26-27 of the present specification. Thus, applicants' disclosure clearly indicates that stabilization of the supramolecular complexes of the invention is the result of the aggregate effects of the interaction between the opposite charges of the block copolymer and the surfactant, as well as the interaction between the hydrophobic groups present on the charged surfactant.

In summary, applicants' position with respect to the rejection of claims 1-18 based on 35 U.S.C. §112, second paragraph, is that any person skilled in the art, having applicants' disclosure and claims before him or her, would be apprised, to a reasonable degree of certainty, as to the exact subject matter encompassed within claims 1-18. Nothing more is required under 35 U.S.C. §112, second paragraph.

For the foregoing reasons, it is clear that, in the present case, the Examiner has failed to satisfy her burden of proof with respect to the §112, second paragraph, rejection of claims 1-18 as set forth in the August 1, 2001 Official Action. Accordingly, this ground of rejection is improper and should be withdrawn.

B. The Combined Disclosures of Hubbell, Ahmad, Nakayama and Weiner Fail to Render Obvious the Subject Matter of Claims 1-18

Applicant respectfully submits that the various references applied against claims 1-18 in the August 1, 2001 Official Action fail to establish a *prima facie* case of obviousness. According to M.P.E.P. § 2143,

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> **The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure.**

(*Emphasis added.*)

The present invention is directed to a composition for delivery of biological agents and to their method of preparation. The composition comprises a supramolecular complex which includes as constitutes (1) a block copolymer having at least one nonionic, water soluble segment and at least one polyionic segment and (2) at least one charged surfactant having hydrophobic groups. The claims specify that the charge of the surfactant component is opposite to the charge of the polyionic segment of the block co-polymer component. The claims further recite that the composition is bound by the interaction between

(i) the opposite charges of the block co-polymer and surfactant components and (ii) the hydrophobic groups of the surfactant.

Unlike the supramolecular complex of the present invention, Hubbell relates to photopolymerizable, biodegradable hydrogels which are purportedly useful as controlled release carriers, among other things. The hydrogels of Hubbell have fundamentally different structures as compared to the block co-polymers utilized in applicants' invention. "Hydrogel", as defined in Grant & Hackh's Chemical Dictionary 5th Ed., at 291 (copy attached), is a water-swellable, rigid, three-dimensional network composed of cross-linked hydrophillic molecules. The cross-linked nature of Hubbell's hydrogel is evidenced from both the specification and claims of the Hubbell patent. See Col. 8, lines 8-12 and Claim 1, lines 5-7. The presence of cross-linked or entangled polymer chains inhibits diffusion of the hydrogel polymer chains in solution. Block co-polymers, on the other hand, as called for in applicants' claims are not cross-linked or otherwise entangled and are free to diffuse in solution. The structure of block co-polymers is illustrated in L.H. Sperling, Introduction to Physical Polymer Science, J. Wiley & Sons, New York, NY (1992), at 46-47, (copy attached).

(2)

Ahmad describes a pharmaceutical composition for aiding human digestion which includes papain, hyssop and grapefruit extract, as active agents, blended together, in preferred embodiments, with a gum base. There is no reason to infer from the disclosure of Ahmad that any benefit would be obtained from

(3)

incorporating the pharmaceutical composition described therein in a controlled release carrier of the type described by Hubbell.

(4) Nakayama relates to a method for stabilizing an agent for contact lens cleaning and sterilization containing a proteolytic enzyme, such as papain among others, by the addition of a surfactant selected from the group of anionic surfactants, amphoteric surfactants and nonionic surfactants. Those of ordinary skill in the art would not consider a disclosure relating to contact lens agents as being of any assistance where, as in this case, a polymer-based composition for facilitating delivery of biological agents is desired.

Appl. argue individual art rej.

Weiner relates to non-toxic, parenteral emulsions for delivery of a bioactive agents, such as drugs, imaging agents or diagnostic agents. According to one embodiment, a water and oil emulsion is provided which comprises a first HLB requirement amount of primary surfactant DOPE, which may further include a second HLB requirement amount of a second surfactant, such as DOPC. As neither Hubbell, nor Ahmad nor Nakayama relate to parenteral emulsions, there is no reason to incorporate a nonionic surfactant, such as DOPE and DOPC, in the compositions disclosed in any of those references in order to impart a wider range of HLB values, which is the stated objective of Weiner. (See Col. 2, lines 10-14).

Regarding the first criterion of *prima facie* obviousness, i.e., suggestion or motivation to combine the cited prior art disclosures, the present case has notable similarities

to Ex parte Levengood, 28 U.S.P.Q.2d 1300 (B.P.A.I. 1993). In reversing a §103 rejection based on a combination of prior art references, the Board in Levengood stated, at 1302:

> ...[A]n examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done.

Here, as in Levengood, the references cited as evidence of obviousness fall far short of providing the "motivation" or "suggestion" to assemble their teachings into a viable invention. There is certainly no motivation apparent from the cited references themselves for combining a block copolymer, having at least one nonionic, water soluble segment and at least one polyionic segment, with at least one charged surfactant having hydrophobic groups, such that the charge of the surfactant is opposite to the charge of polyionic segment of the block copolymer, to form a supramolecular complex useful for delivery of biological agents. Consequently, the first criterion for a case of *prima facie* obviousness has not been established.

As for the reasonable expectation of success criterion, since none of the references of record even remotely suggest applicants' composition for facilitating delivery of biological agents, comprising a block copolymer having at least one non-ionic, water soluble segment and at least one polyionic segment and at least one charged surfactant having hydrophobic groups, with the charge of the surfactant being opposite to the charge

of the polyionic segment of the block copolymer and the method of preparing such composition, it necessarily follows that the prior art does not provide the requisite reasonable expectation of success.

Turning to the third criterion of the *prima facie* case, the references proposed to be combined in support of this ground of rejection clearly fail to teach or suggest all of applicants' claim recitations. As previously noted, there is no disclosure or suggestion in any of the cited references of a composition for delivery of biological agents having a block copolymer with at least one nonionic, water soluble segment and at least one polyionic segment as a component thereof. Nor is there any appreciation evidenced in any of the cited references that the charge of the surfactant component is opposite to the charge of the polyionic segment of the block copolymer. On the contrary, according to Nakayama, nonionic surfactants, anionic surfactants or amphoteric surfactants made be used interchangeably for the purpose of stabilizing the proteolytic enzyme-containing contact lens agents described therein. Such disclosure unquestionably fails to render obvious applicants' claims that call for the combination of a block copolymer which has a polyanionic segment with a cationic surfactant having hydrophobic groups. See, for example, claim 4 and the claims dependent therefrom.

Moreover, there is nothing in the prior art references cited in support of this obviousness rejection to suggest the modifications thereof that would be necessary to satisfy all of

the recitations of applicants' claims. Such modifications would include, at a minimum, substituting a block copolymer for the hydrogels of Hubbell. However, hydrogels having cross-linked polymer chains are an essential aspect of the Hubbell invention. It is well established that a patent disclosure cannot properly be modified if the effect would be to destroy the invention on which the patent is based. Cf. Ex parte Hartman, 186 U.S.P.Q. 366 (Bd. Apps. 1974). Likewise, there is no teaching or suggestion in any of the cited references that would provide incentive for combining a block copolymer comprising at least one polyionic segment with a surfactant having hydrophobic groups and a charge which is opposite to that of the polyionic segment of the block copolymer, thereby resulting in supramolecular complexes formed due to interactions between such opposite charges and the hydrophobic groups of the surfactant.

For all of the above reasons, the combined disclosures of Hubbell, Ahmad, Nakayama and Weiner fail to provide a proper basis for concluding that the present invention is *prima facie* obvious.

Given that the prior art references cited in support of the §103(a) rejection of claims 1-18 fail to teach of suggest the claimed subject matter as a whole, no evidence of surprising or unexpected result need be presented. In re Lunsford, 148 U.S.P.Q. 721 (C.C.P.A. 1966).

The obviousness rejection set forth in the May 22, 2001 Official Action is a clear case of hindsight reconstruction of

the claimed invention. It is quite apparent that the Examiner has used applicants' disclosure as a guide for combining unrelated prior art teachings in an effort to make out a case of obviousness. Such hindsight reconstruction has long been held impermissible, since it is contrary to the standard of obviousness set forth in 35 U.S.C. §103, which requires a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made, based on the state of the art as reflected in the cited references, and without benefit of applicants' disclosure. None of the diverse references relied on by the Examiner in formulating the §103 rejection in this case contains the slightest suggestion to use what is disclosed in one reference in combination with what is disclosed in the other references. Cf. In re Avery, 186 U.S.P.Q. 161 (C.C.P.A. 1975). That being the case, it cannot reasonably be maintained that the combined disclosures of Hubbell, Ahmad, Nakayama and Weiner fairly suggest doing what the applicant has done. Accordingly, the rejection under 35 U.S.C. §103 based on the combination of these four (4) references is improper. In re Shaffer, 108 U.S.P.Q. 326 (C.C.P.A. 1956).

C. The 35 U.S.C. §101 Double Patenting Rejection of Claims 2-5, 7-12, 14 and 15 is Improper and Should be Withdrawn

A "same invention" double patenting rejection under 35 U.S.C. §101 is proper only when the applicants are attempting to twice claim identical subject matter. Because there are

embodiments of applicants' invention that fall within the scope of the claims of the co-pending '653 application, but not within the scope of claims 2-5, 7-12, 14 and 15 of the present application, it is clear that applicants are not attempting to claim identical subject matter twice. It is significant to note in this regard that the claims identified as allegedly violating §101 are all dependent claims. As such, these claims must be construed to incorporate by reference all the limitations of the claims to which they refer. When properly construed, the claims of the present invention, which are drawn to a two component supramolecular complex, as noted above, could be literally infringed without literally infringing corresponding claims in the '653 application, which also call for a therapeutic or diagnostic agent in combination with the aforementioned supramolecular complex.

In view of the clear difference in claim scope between the respective applications, statutory double patenting does not exist in the present case. See §804 of the Manual of Patent Examining Procedure (M.P.E.P.).

D. A Provisional Obviousness-Type Double Patenting Rejection is Inappropriate in the Present Case Because the Effective Filing Date of the Application on Which the Rejection is Based is the Same as the Present Application

As noted in M.P.E.P. §804, an obviousness-type double patenting rejection is grounded in public policy so as to prevent the unjustified or improper timewise extension of the right to

exclude granted by a patent. In this case, however, there is no opportunity for unjustified or improper timewise extension of exclusive patent rights. Both of the applications in question have the same effective filing date, i.e. June 11, 1998. Thus, if patents were granted on these applications, the patent terms would expire on the same date. That being the case, there is no basis for an obviousness-type double patenting rejection in the present case.

OK withdrawn Obv. D.P.

In any event, if the Examiner is inclined to maintain this ground of rejection, it is hereby requested that it be held in abeyance until such time as it is the only rejection remaining in the application, whereupon it should be withdrawn so that either the present application or the '653 application may be passed to issue, with the provisional double patenting rejection being converted to a non-provisional double patenting rejection in the other application, as authorized by §804 of the M.P.E.P.

The Examiner is correct in assuming at page 6 of the August 1, 2001 Official Action, that the subject matter of the various claims was commonly owned at the time the invention covered thereby was made.

In view of the foregoing remarks, it is respectfully urged that the rejections and objection set forth in the August 1, 2001 Official Action be withdrawn and that this application be passed to issue and such action is earnestly solicited.

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Enclosures

MARKED-UP VERSION OF AMENDED CLAIMS

8. (Amended) A composition as claimed in claim 4, wherein said polyanionic segment is a homopolymer or a co-polymer prepared from a monomer which polymerizes to form a product with carboxyl pendant groups, said monomer being selected from the group consisting of acrylic acid, [asparatic] aspartic acid (amino acid), 1,4-phenylenediacrylic acid citraconic acid, citraconic anhydride, trans cinnamic acid, 4-hydroxy-3-methoxy cinnamic acid, p-hydroxy cinnamic acid, trans-glutaconic acid, [glutaminc] glutamic acid (amino acid), itaconic acid, linoleic acid, linolenic acid, methacrylic acid, maleic acid, maleic anhydride, mesaconic acid, trans-β-hydromuconic acid, trans-trans muconic acid, oleic acid, ricinoleic acid, 2-propene-1-sulfonic acid, 4-styrene sulfonic acid, trans-traumatic acid, vinylsulfonic acid, vinyl phospate acid, vinyl benzoic acid, vinyl glycolic acid.

11. (Amended) A composition as claimed in claim 10, wherein said nonionic surfactant is selected from the group consisting of [dioloeoyl] dioleoyl phosphatidylethanolamine, dioleoyl phosphatidylcholine, or a mixture of said nonionic surfactants.

15. (Amended) A composition as claimed in claim 12, [wherein said] comprising an anionic surfactant [is] selected from the group consisting of alkyl sulfates, alkyl sulfonates, fatty acid soaps, salts of hydrox-, hydroperoxy-, polyhydroxy-, epoxy- fatty acids, salts of mono- and polycarboxylic acids, prostanoic acid and [prostaglandines] prostaglandins, [leukotriens] leukotrienes and lipoxines, alkyl phosphates, alkyl phosphonates, lipids, sodium-dialkyl sufosuccinate, n-alkyl ethoxylated sulfates, cholate and desoxycholate of bile salts, perfluorocarboxylic acids, fluoroaliphatic phosphonates, fluoroaliphatic suphates.